**WelChol® Tablets**
**(colesevelam hydrochloride)**
**[koe le sev´ e lam]**

## DESCRIPTION

WelChol® contains colesevelam hydrochloride (hereafter referred to as colesevelam), a non-absorbed, polymeric, lipid-lowering agent intended for oral administration. Colesevelam is a high capacity bile acid binding molecule. Colesevelam is poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide. Colesevelam is hydrophilic, and insoluble in water.
WelChol® is an off-white, film-coated, solid tablet containing 625 mg colesevelam. In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, silicon dioxide, HPMC (hydroxypropyl methylcellulose), and acetylated monoglyceride. The tablets are imprinted using a water-soluble black ink.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

The mechanism of action for the lipid-lowering activity of colesevelam, the active pharmaceutical ingredient in WelChol®, has been evaluated in various *in vitro* and *in vivo* studies. These studies have demonstrated that colesevelam binds bile acids, including glycocholic acid, the major bile acid in humans.
Cholesterol is the sole precursor of bile acids. During normal digestion, bile acids are secreted into the intestine. A major portion of bile acids are then absorbed from the intestinal tract and returned to the liver via the enterohepatic circulation.
Colesevelam is a non-absorbed, lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-$\alpha$-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein (LDL) receptors. These compensatory effects result in increased clearance of LDL cholesterol (LDL-C) from the blood, resulting in decreased serum LDL-C levels.[1, 2] Serum triglyceride levels may increase or remain unchanged.

Clinical studies have demonstrated that elevated levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (Apo B, a protein associated with LDL-C) are associated with an increased risk of atherosclerosis in humans. Similarly, decreased levels of high-density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis[1]. Epidemiological investigations have established that cardiovascular morbidity and mortality vary directly with the levels of total-C and LDL-C, and inversely with the level of HDL-C.
The combination of colesevelam and an HMG-CoA reductase inhibitor is effective in further lowering serum total-C and LDL-C levels beyond that achieved by either agent alone. The effects of colesevelam either alone or with an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been determined.

**Pharmacokinetics**

Colesevelam is a hydrophilic, water-insoluble polymer that is not hydrolyzed by digestive enzymes and is not absorbed. In 16 healthy volunteers, an average of 0.05% of a single $^{14}$C-labeled colesevelam dose was excreted in the urine when given following 28 days of chronic dosing of 1.9 grams of colesevelam twice per day.

**Clinical Trials**

WelChol® reduces total-C, LDL-C, and Apo B, and increases HDL-C when administered either alone or in combination with an HMG-CoA reductase inhibitor in patients with primary hypercholesterolemia.

Approximately 1400 patients were studied in eight clinical trials with treatment durations ranging from 4 to 50 weeks. With the exception of one long-term study, all studies were multicenter, randomized, double-blind, and placebo-controlled. A maximum therapeutic response to WelChol® was achieved within 2 weeks and was maintained during long-term therapy.

In a study in patients with LDL-C between 130 and 220 mg/dL (mean 158 mg/dL), WelChol®™ was given for 24 weeks in divided doses with the morning and evening meals. As shown in Table 1 below, the mean LDL-C reductions were 15% and 18% at the 3.8 g and 4.5 g doses. The respective mean total-C reductions were 7% and 10%. The mean Apo B reductions were 12% in both treatment groups. WelChol® at both doses increased HDL-C by 3%. There were small increases in triglycerides (TG) at both WelChol® doses that were not statistically different from placebo.

**Table 1: WelChol® 24 Week Trial - Percentage Change in Lipid Parameters From Baseline**

| GRAMS/DAY | N | TOTAL-C | LDL-C | APO B | HDL-C | NON-HDL-C | TG |
|---|---|---|---|---|---|---|---|
| Placebo | 88 | +1 | 0 | 0 | –1 | +1 | +5 |
| 3.8 g (6 tablets) | 95 | –7* | –15* | –12* | +3* | -10* | +10 |
| 4.5 g (7 tablets) | 94 | –10* | –18* | –12* | +3 | -13* | +9 |

*p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline
LDL-C, total-C, and Apo B are mean values; HDL-C and TG are median values.

In a study in 98 patients with LDL-C between 145 and 250 mg/dL (mean 169 mg/dL), WelChol® 3.8 g was given for 6 weeks as a single dose with breakfast, a single dose with dinner, or as divided doses with breakfast and dinner. The mean LDL-C reductions were 18%, 15%, and 18% for the three dosing regimens, respectively. The reductions with these three regimens were not statistically different from one another.

Co-administration of WelChol® and an HMG-CoA reductase inhibitor (atorvastatin, lovastatin, or simvastatin) demonstrated an additive reduction of LDL-C in three clinical studies. As demonstrated in Table 2 below, WelChol® doses of 2.3 g to 3.8 g resulted in additional 8% to 16% reductions in LDL-C above that seen with the HMG-CoA reductase inhibitor alone.

**Table 2: WelChol® in Combination with Atorvastatin, Simvastatin, and Lovastatin –Percentage Change in Lipid Parameters**

| DOSE/DAY | N | TOTAL-C | LDL-C | APO B | HDL-C | NON-HDL-C | TG |
|---|---|---|---|---|---|---|---|
| **Atorvastatin Trial (4-week)** | | | | | | | |
| Placebo | 19 | +4 | +3 | -3 | +4 | +4 | +10 |
| Atorvastatin 10 mg | 18 | –27* | –38* | –32* | +8 | -35* | –24* |
| WelChol® 3.8 g/ Atorvastatin 10 mg | 18 | –31* | –48* | –38* | +11 | -40* | –1 |
| Atorvastatin 80 mg | 20 | –39* | –53* | –46* | +6 | -50* | –33* |
| **Simvastatin Trial (6-week)** | | | | | | | |
| Placebo | 33 | –2 | –4 | –4* | –3 | -2 | +6 |
| Simvastatin 10 mg | 35 | –19* | –26* | –20* | +3* | -24* | –17* |
| WelChol® 3.8 g/ Simvastatin 10 mg | 34 | –28* | –42* | –33* | +10* | -37* | –12* |
| Simvastatin 20 mg | 39 | –23* | –34* | –26* | +7* | -30* | –12* |
| WelChol® 2.3 g/ Simvastatin 20 mg | 37 | –29* | –42* | –32* | +4* | -37* | –12* |
| **Lovastatin Trial (4-week)** | | | | | | | |
| Placebo | 26 | +1 | 0 | 0 | +1 | +1 | +1 |
| Lovastatin 10 mg | 26 | –14* | –22* | –16* | +5 | -19* | 0 |
| WelChol® 2.3 g/ Lovastatin 10 mg together | 27 | –21* | –34* | –24* | +4 | -27* | –1 |
| WelChol® 2.3 g/ Lovastatin 10 mg apart | 23 | –21* | –32* | –24* | +2 | -28* | –2 |

*p<0.05 for lipid parameters compared to placebo, for Apo B compared to baseline

**LDL-C, TOTAL-C AND APO B ARE MEAN VALUES; HDL-C AND TG ARE MEDIAN VALUES.**

**IN ALL THREE STUDIES, THE LDL-C REDUCTION ACHIEVED WITH THE COMBINATION OF WELCHOL® AND ANY GIVEN DOSE OF HMG-COA REDUCTASE INHIBITOR THERAPY WAS STATISTICALLY SUPERIOR TO THAT ACHIEVED WITH WELCHOL® OR THAT DOSE OF THE HMG-COA REDUCTASE INHIBITOR ALONE.**

**THE LDL-C REDUCTION WITH ATORVASTATIN 80 MG WAS NOT STATISTICALLY SIGNIFICANTLY DIFFERENT FROM THE COMBINATION OF WELCHOL® 3.8 G AND ATORVASTATIN 10 MG.**

**INDICATIONS AND USAGE**

WelChol®, administered alone or in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet and exercise for the reduction of elevated LDL cholesterol in patients with primary hypercholesterolemia (Fredrickson Type IIa).
Therapy with lipid lowering agents should be a component of multiple risk-factor intervention in patients at significant increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid altering agents should be used in addition to a diet restricted in saturated fat and cholesterol and when the response to diet and other non-pharmacological means has been inadequate.
Prior to initiating therapy with WelChol®, secondary causes of hypercholesterolemia (i.e., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile obtained to assess total-C, HDL-C, and TG. For individuals with TG less than 400 mg/dL, LDL-C can be estimated using the following equation.[3]
LDL-C = Total-C − [(TG/5) + HDL-C]

Periodic determination of serum cholesterol levels in patients as outlined in the National Cholesterol Education Program (NCEP) guidelines should be done to confirm a favorable initial and long-term response. The NCEP treatment guidelines are presented in Table 3.

**Table 3: NCEP Guidelines**

| RISK CATEGORY | LDL-C GOAL | LDL LEVEL AT WHICH TO INITIATE THERAPEUTIC LIFESTYLE CHANGES (TLC) | LDL LEVEL AT WHICH TO CONSIDER DRUG THERAPY |
|---|---|---|---|
| CHD or CHD Risk Equivalents (10-year risk >20%) | <100 mg/dL | ≥100 mg/dL | ≥130 mg/dL (100-129 mg/dL: drug optional)* |
| 2+ Risk Factors (10-year risk ≤20%) | <130 mg/dL | ≥130 mg/dL | 10-year risk 10-20%: ≥130 mg/dL |
| | | | 10-year risk <10%: ≥160 mg/dL |
| 0-1 Risk Factor† | <160 mg/dL | ≥160 mg/dL | ≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional) |

* Some authorities recommend use of LDL cholesterol-lowering drugs in the category if LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL cholesterol e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

**Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals***

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or an anti-hypertensive medication)
- Low HDL cholesterol (<40 mg/dL) †
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)

* In ATP III, diabetes is regarded as a CHD risk equivalent.

† HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.

After the LDL-C goal has been achieved, if the TG is still ≥200mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

## CONTRAINDICATIONS

WelChol® is contraindicated in individuals with bowel obstruction and in individuals who have shown hypersensitivity to any of the components of WelChol®.

## PRECAUTIONS

### General

Patients with TG levels greater than 300 mg/dL were excluded from WelChol® clinical trials. Caution should be exercised when treating patients with TG levels greater than 300 mg/dL.
In non-clinical safety studies, rats administered colesevelam at doses greater than 30-fold the projected human clinical dose experienced hemorrhage from vitamin K deficiency. WelChol® did not induce any clinically significant reduction in the absorption of vitamins A, D, E, or K during clinical trials of up to one year. However, caution should be exercised when treating patients with a susceptibility to vitamin K or fat soluble vitamin deficiencies.
The safety and efficacy of WelChol® in patients with dysphagia, swallowing disorders, severe gastrointestinal motility disorders, or major gastrointestinal tract surgery have not been established. Consequently, caution should be exercised when WelChol® is used in patients with these gastrointestinal disorders.

### Information for the Patient

WelChol® may be taken once per day with a meal, or taken twice per day in divided doses with meals. Patients should be directed to take WelChol® with a liquid and a meal, and adhere to their NCEP-recommended diet. Patients should tell their physicians if they are pregnant, are intending to become pregnant, or are breastfeeding.

### Laboratory Tests

Serum total-C, LDL-C and TG levels should be determined periodically based on NCEP guidelines to confirm favorable initial and adequate long-term responses.

### Drug Interactions

WelChol® has been studied in several human drug interaction studies in which it was administered with a meal and the test drug. WelChol® was found to have no significant effect on the bioavailability of digoxin, fenofibrate, lovastatin, metoprolol, quinidine, valproic acid, and warfarin. WelChol® decreased the Cmax and AUC of sustained-release verapamil (Calan SR®) by approximately 31% and 11%, respectively. Since there is a high degree of variability in the bioavailability of verapamil, the

clinical significance of this finding is unclear. In clinical studies, co-administration of WelChol® with atorvastatin, lovastatin, or simvastatin did not interfere with the lipid-lowering activity of the HMG-CoA reductase inhibitor. Other drugs have not been studied. When administering other drugs for which alterations in blood levels could have a clinically significant effect on safety or efficacy, physicians should consider monitoring drug levels or effects.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A 104-week carcinogenicity study with colesevelam (WelChol®) was conducted in CD-1 mice, at oral dietary doses up to 3 g/kg/day. This dose was approximately 50 times the maximum recommended human dose of 4.5 g/day, based on body weight, mg/kg. There were no significant drug-induced tumor findings in male or female mice. In a 104-week carcinogenicity study with colesevelam (WelChol®) in Harlan Sprague-Dawley rats, a statistically significant increase in the incidence of pancreatic acinar cell adenoma was seen in male rats at doses >1.2 g/kg/day (approximately 20 times the maximum human dose, based on body weight, mg/kg) (trend test only). A statistically significant increase in thyroid C-cell adenoma was seen in female rats at 2.4 g/kg/day (approximately 40 times the maximum human dose, based on body weight, mg/kg).
Colesevelam and four degradants present in the drug substance have been evaluated for mutagenicity in the Ames test and a mammalian chromosomal aberration test. The four degradants and an extract of the parent compound did not exhibit genetic toxicity in an *in vitro* bacterial mutagenesis assay in *S. typhimurium* and *E. coli* (Ames assay) with or without rat liver metabolic activation. An extract of the parent compound was positive in the Chinese Hamster Ovary (CHO) cell chromosomal aberration assay in the presence of metabolic activation and negative in the absence of metabolic activation. The results of the CHO cell chromosomal aberration assay with two of the four degradants, decylamine HCl and aminohexyltrimethyl ammonium chloride HCl, were equivocal in the absence of metabolic activation and negative in the presence of metabolic activation. The other two degradants, didecylamine HCl and 6-decylamino-hexyltrimethyl ammonium chloride HCl, were negative in the presence and absence of metabolic activation.
Colesevelam did not impair fertility in rats at doses of up to 3 g/kg/day (approximately 50 times the maximum human dose, based on body weight, mg/kg).

**PREGNANCY**

**Pregnancy Category B**

Reproduction studies have been performed in rats and rabbits at doses up to 3 g/kg/day and 1 g/kg/day, respectively (approximately 50 and 17 times the maximum human dose, based on body weight, mg/kg) and have revealed no evidence of harm to the fetus due to colesevelam. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Requirements for vitamins and other nutrients are increased in pregnancy. The effect of WelChol® on the absorption of vitamins has not been studied in pregnant women.

**Pediatric Use**

The safety and efficacy of colesevelam (WelChol® ) have not been established in pediatric patients.

**Geriatric Use**

There is no evidence for special considerations when colesevelam (WelChol® ) is administered to elderly patients.

**ADVERSE REACTIONS**

WelChol® treatment-emergent adverse events that occurred in greater than 2% of patients in an integrated safety analysis are presented in Table 4.

**Table 4: Frequent (>2%) Treatment-Emergent Adverse Events By Treatment Category**

| BODY SYSTEM/ ADVERSE EVENT | PLACEBO (N=258) % | WELCHOL® ONLY (N=807) % |
|---|---|---|
| **Body as a Whole** | | |
| Infection | 13 | 10 |
| Headache | 8 | 6 |
| Pain | 7 | 5 |
| Back Pain | 6 | 3 |
| Abdominal Pain | 5 | 5 |
| Flu Syndrome | 3 | 3 |
| Accidental Injury | 3 | 4 |
| Asthenia | 2 | 4 |
| **Digestive System** | | |
| Flatulence | 14 | 12 |
| Constipation | 7 | 11 |
| Diarrhea | 7 | 5 |
| Nausea | 4 | 4 |
| Dyspepsia | 3 | 8 |
| **Respiratory System** | | |
| Sinusitis | 4 | 2 |
| Rhinitis | 3 | 3 |
| Cough Increased | 2 | 2 |
| Pharyngitis | 2 | 3 |
| **Musculoskeletal System** | | |
| Myalgia | 0 | 2 |

## OVERDOSAGE

Because WelChol® is not absorbed, the risk of systemic toxicity is low. Doses in excess of 4.5 g per day have not been tested.

## DOSAGE AND ADMINISTRATION

### Monotherapy

The recommended starting dose of WelChol® is 3 tablets taken twice per day with meals or 6 tablets once per day with a meal. The WelChol® dose can be increased to 7 tablets, depending upon the desired therapeutic effect. WelChol® should be taken with a liquid.

### Combination Therapy

WelChol®, at doses of 4 to 6 tablets per day, has been shown to be safe and effective when dosed at the same time (i.e., co-administered) as an HMG-CoA reductase inhibitor or when the two drugs are dosed apart. [**CLINICAL PHARMACOLOGY, Clinical Trials**]. WelChol® should be taken with a liquid. For maximal therapeutic effect in combination with an HMG-CoA reductase inhibitor, the recommended dose of WelChol® is 3 tablets taken twice per day with meals or 6 tablets taken once per day with a meal.

## HOW SUPPLIED

WelChol® (colesevelam hydrocholoride), 625 mg, is supplied as an off-white, solid tablet imprinted with the word "Sankyo" over "C01".
WelChol® Tablets are available as follows:
Bottles of 180—NDC 65597-701-18
Bottles of 24 – NDC 65597-701-24

### Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Brief exposure to 40 °C does not adversely affect the product. Protect from moisture.

### References

1. Grundy SM, Ahrens EH, Salen G. Interruption of the enterohepatic circulation of bile acids in man: comparative effects of cholestyramine and ileal exclusion on cholesterol metabolism. J Lab Clin Med 1971; 78: 94-121.

2. Shepherd J, Packard CJ, Bicker S, Veitch LTD, Gemmell MH. Cholestyramine promotes receptor-mediated low-density-lipoprotein catabolism. N Engl J Med 1980; 302: 1219-22.

3. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of LDL cholesterol in plasma without use of a preparative ultracentifuge. Clin. Chem. 1972; 18(6): 499.

**Manufactured for:** Sankyo Pharma Inc.
Parsippany, New Jersey 07054
**by:** Patheon YM Inc.
Toronto, Ontario M3B 1Y5
**Active Ingredient**: Product of Austria
**Licensed From:** GelTex Pharmaceuticals, Inc.

**Rx Only**
**Issued:**
**Version:** 7